# Neuroimaging and Neurodevelopmental Outcome in Extremely Preterm Infants

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abstract

**BACKGROUND:** Extremely preterm infants are at risk for neurodevelopmental impairment (NDI). Early cranial ultrasound (CUS) is usual practice, but near-term brain MRI has been reported to better predict outcomes. We prospectively evaluated MRI white matter abnormality (WMA) and cerebellar lesions, and serial CUS adverse findings as predictors of outcomes at 18 to 22 months' corrected age.

**METHODS:** Early and late CUS, and brain MRI were read by masked central readers, in a large cohort ($n$ = 480) of infants <28 weeks' gestation surviving to near term in the Neonatal Research Network. Outcomes included NDI or death after neuroimaging, and significant gross motor impairment or death, with NDI defined as cognitive composite score <70, significant gross motor impairment, and severe hearing or visual impairment. Multivariable models evaluated the relative predictive value of neuroimaging while controlling for other factors.

**RESULTS:** Of 480 infants, 15 died and 20 were lost. Increasing severity of WMA and significant cerebellar lesions on MRI were associated with adverse outcomes. Cerebellar lesions were rarely identified by CUS. In full multivariable models, both late CUS and MRI, but not early CUS, remained independently associated with NDI or death (MRI cerebellar lesions: odds ratio, 3.0 [95% confidence interval: 1.3–6.8]; late CUS: odds ratio, 9.8 [95% confidence interval: 2.8–35]), and significant gross motor impairment or death. In models that did not include late CUS, MRI moderate-severe WMA was independently associated with adverse outcomes.

**CONCLUSIONS:** Both late CUS and near-term MRI abnormalities were associated with outcomes, independent of early CUS and other factors, underscoring the relative prognostic value of near-term neuroimaging.

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**WHAT'S KNOWN ON THIS SUBJECT:** White matter abnormality (WMA) on neuroimaging is considered a crucial link with adverse neurodevelopmental outcome in preterm infants. Brain MRI is more sensitive in detecting WMA than cranial ultrasound (CUS), but questions remain about timing and prognostic value of modalities.

**WHAT THIS STUDY ADDS:** Near-term CUS and MRI abnormalities were associated with adverse 18- to 22-month outcomes, independent of early CUS and other factors, underscoring the relative prognostic value of later neuroimaging in this large, extremely preterm cohort surviving to near-term.

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Cranial ultrasound (CUS) is currently the routine neuroimaging tool for preterm infants.[1] Adverse neurodevelopmental outcomes, including cerebral palsy (CP), have been shown to be associated with major CUS abnormalities in very preterm infants,[2] but studies vary widely with regard to CUS protocols and timing. Carefully performed CUS and outcomes studies among very preterm infants have implicated white matter (WM) injury, not intracranial hemorrhage (ICH) alone, as a critical underlying finding linking abnormal CUS findings with adverse neurodevelopmental outcome.[3–5] This, in part, has led to the concept that if WM injury is better characterized, it may be possible to better predict motor and developmental outcomes, anticipate needs, and devise preventative interventions.

Brain MRI is more sensitive in detecting WM abnormalities (WMAs) than CUS.[6,7] WM injury on near-term MRI in preterm infants has been associated with brain maturational disturbances, as well as developmental and neuromotor impairments.[8–10] Cerebellar injury seen by MRI but not by CUS may be associated with higher risk for neurologic abnormalities,[11] although the importance of punctate lesions is unclear.[12]

Despite what appears to be extensive experience with CUS and brain MRI in preterm infants, controversies and questions remain as to which neuroimaging studies to perform, when to perform them, and their relative values in prognosis. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) developed the Neuroimaging and Neurodevelopmental Outcomes (NEURO) study, which is, to our knowledge, the largest prospective study of serial neonatal CUS, near-term brain MRI, and neurodevelopmental outcomes in extremely preterm infants. Our objectives were to (1) relate near-term brain MRI findings of WMA and cerebellar lesions, and early and late CUS adverse findings to neurodevelopmental outcomes at 18 to 22 months' corrected age, and (2) assess the relative value of early CUS, late CUS, and MRI, considering other perinatal/neonatal risk factors, to predict outcomes.

## METHODS

### Study Design and Population

The NEURO study was a secondary study to the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT; NCT00233324), a randomized, multicenter, 2 × 2 factorial trial of ventilation and oxygenation management strategies among 24 to 27+6/7 week estimated gestational age (EGA) infants.[13,14] Infants eligible for the NEURO study were enrolled in SUPPORT at 1 of the 16 centers participating in the NEURO secondary. The SUPPORT trial enrolled infants born February 2005 to February 2009, from 20 NRN centers. The NEURO study was approved and began recruitment after SUPPORT began enrollment, and participating centers did not launch simultaneously. The serial neuroimaging in the NEURO study continued to near-term or term equivalent age; therefore, this cohort represents a selective subgroup of the SUPPORT cohort. Written informed consent to participate in NEURO was obtained at the time of enrollment into SUPPORT, or separately. The study was approved by the institutional review boards of all participating centers, and by the institutional review board of RTI International (Data Coordinating Center for the NRN).

Trained research staff at each center collected maternal, demographic, perinatal, and neonatal data by using common definitions that were developed by NICHD NRN investigators and described in previous publications.[13–16] Data were transmitted to the NRN Data Coordinating Center at RTI International, which stored, managed, and analyzed all data.

### Neuroimaging: CUS and Brain MRI

#### *Cranial Ultrasound*

An "early" CUS at 4 to 14 days, and a "late" CUS at 35 to 42 weeks' postmenstrual age (PMA) were obtained for NEURO study participants. CUS imaging was per local center clinical protocol. Mastoid, posterior fossa, or cine views were not specifically required. Central reader interpretations were used for study analyses. Two masked central readers (Drs Bulas and Slovis) reviewed all CUS independently, utilizing a modified central reading form used in previous studies.[17] A composite adverse finding on early CUS was defined as presence of grade III or IV ICH[18] or cystic periventricular leukomalacia (cPVL) on either or both sides. A composite adverse finding on late CUS was defined as cPVL, or porencephalic cyst, or moderate-to-severe ventricular enlargement (VE, with moderate and severe VE defined as ventricular-to-brain ratio of 1:3 to 2:3 and >2:3, respectively)[19,20] on either or both sides, or shunt. For all CUS, interobserver reliability between central readers demonstrated $\kappa = 0.75$ for early CUS adverse finding, and $\kappa = 0.88$ for late CUS adverse finding. Central readers also noted additional views including mastoid views, and presence of cerebellar or posterior fossa lesions.

#### *Brain MRI*

A conventional brain MRI was obtained at 35 to 42 weeks' PMA, ideally within 7 days of the late CUS. For the purposes of this analysis, infants for whom MRIs were obtained within 2 weeks of late CUS were included. Minimum requirements included using a 1.5 T system, and necessary sequences included T1-weighted and T2-weighted sagittal

and axial views, section thickness 3 mm and 0 gap; coronal SPGR (spoiled gradient recalled acquisition), and axial GRE (gradient recalled echo). In the context of the NEURO study, it was advised that neonatal brain MRIs could be obtained without the use of sedation. Central reader interpretations were used for study analyses. A masked central reader (Dr Barnes) reviewed all brain MRIs utilizing a central reader form that included WMA scoring according to a widely used classification system,[6,8,21] using 5 areas of WM assessment including (1) extent of WM signal abnormality, (2) periventricular WM volume loss, (3) cystic abnormalities, (4) ventricular dilatation, and (5) thinning of the corpus callosum.[8] Interrater agreement for moderate or severe WMA by using this classification system has been reported to be 96% to 98%.[8,21] The central reader form also collected information regarding location, number, size, and imaging characteristics of lesions. Significant cerebellar lesions were defined as lesions that were bilateral, cystic, and/or lesions that were ≥4 mm in size. Adverse findings on brain MRI were defined as moderate or severe WMA, and/or significant cerebellar lesions.

### Neurodevelopmental Follow-up Assessments

At 18 to 22 months of age corrected for prematurity, infants underwent a comprehensive neurodevelopmental assessment, as described previously.[22] Neurologic examinations were performed by certified examiners.[23] Gross motor function was assessed with the Gross Motor Function Classification System (GMFCS) in all children.[24] CP was defined as abnormal tone or reflexes in at least 1 extremity and abnormal control of movement or posture to a degree that interferes with age-appropriate activity. Children with CP were defined as having moderate-to-severe CP if they had a GMFCS level ≥2. Cognitive development was assessed by using the Bayley Scales of Infant Development, Third Edition (BSID III),[25] performed by trained, certified examiners. Severe hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and severe visual impairment (defined as vision worse than 20/200) were based on examination and primary caregiver report.

### Outcomes

Neurodevelopmental impairment (NDI) was defined as any of the following: a cognitive composite score on the BSID III <70, moderate-to-severe CP, GMFCS level ≥2, severe hearing impairment, or bilateral severe visual impairment. Significant gross motor impairment was defined as moderate-to-severe CP or GMFCS ≥2, regardless of diagnosis of CP. Minimally impaired/unimpaired was defined as having all of the following: cognitive score >85, no CP, without severe hearing impairment, and without bilateral severe visual impairment. The primary composite outcomes for multivariable analyses were NDI or death after all neuroimaging was obtained, and significant gross motor impairment or death after all neuroimaging. Death was included in the composite outcome because it was a competing outcome that precluded identification of neurologic and developmental outcomes.

### Statistical Analyses

Unadjusted associations were examined by $\chi^2$ test, Fisher's exact test, or analysis of variance. To assess the incremental predictive value of early CUS, late CUS, and MRI findings, we developed a series of generalized linear mixed models to predict the binary outcomes of NDI or death, or of significant gross motor impairment or death. Included in the models were combinations of 4 sets of risk variables, which were defined before analyses: (1) Perinatal/neonatal risk factors: NRN center (entered as a random effect in all models), EGA (24–25+6/7 weeks vs 26–27+6/7 weeks), race, male gender, multiple gestation, maternal insurance (public versus other), late sepsis, bronchopulmonary dysplasia (BPD), postnatal steroids, and surgery for patent ductus arteriosus (PDA) or necrotizing enterocolitis (NEC) or retinopathy of prematurity (ROP). One variable at a time was excluded by backward elimination (lowest $F$ test) until all those remaining had $P$ values < .20, the retained subset was then included in all subsequent models; (2) early CUS composite adverse finding; (3) late CUS composite adverse finding; and (4) MRI adverse findings: moderate-to-severe WMA and significant cerebellar lesions. Results of the models were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We then conducted receiver-operating characteristic (ROC) curve analyses by using these models, and compared the predictive capabilities on the basis of the area under the curve (AUC) of the ROC curves.

## RESULTS

Four hundred eighty infants had complete neuroimaging with late CUS and brain MRI within 2 weeks of each other; imaging occurred within 7 days in 93% of the infants (445 of 480), and within 5 days in 87% (416 of 480). The mean (SD) age at neuroimaging was as follows: early CUS, 8.1 (4.6) days; late CUS, 37.4 (2.3) weeks' PMA; and brain MRI, 37.9 (2.3) weeks' PMA. Only 7 appropriately timed MRIs were excluded because of inadequate MRI quality or movement artifact that precluded interpretation. Fifteen infants died after all neuroimaging was obtained and before 18 months' corrected age, and 20 were lost to follow-up. A BSID III cognitive composite score could be obtained for 441 children, and a neurosensory examination was obtained for 445. Therefore, the

outcome of NDI or death could be determined for 95% of the cohort (456 of 480) and significant gross motor impairment or death for 96% (460 of 480).

Selected demographic, perinatal, and neonatal variables of the NEURO follow-up cohort are shown in Table 1. The rates of early or late CUS adverse findings were low, at 9.7% and 5.8%, as were the rates of NDI and significant gross motor impairment, at 8.6% and 3.8%, respectively. Among the 441 children with a BSID III cognitive composite score, 26 (5.9%) scored <70, 98 (22%) scored <85, and the mean ± SD score was 91.8 ± 14. Among 445 children with neurosensory examinations, moderate-to-severe CP was diagnosed in 13 (2.9%), severe visual impairment in 3 (0.7%), and severe hearing impairment in 8 (1.8%).

Brain MRI findings and outcomes at 18 to 22 months are shown in Tables 2 and 3. Increasing severity of WMA (Table 2) and presence of cerebellar lesions (Table 3) were associated with significantly lower mean BSID III cognitive scores, higher rates of cognitive scores <70 and <85, and moderate-to-severe CP. Among the 5 children with significant gross motor impairment and mild WMA on MRI, none had adverse early or late CUS findings, but 3 had significant cerebellar lesions on MRI. Of note, cerebellar or posterior fossa lesions were seen by early or late CUS in only 7 cases, but mastoid views were included in only 48.2% of early CUS and 46.1% of late CUS, as reported by central readers. Among the 72 cases with cerebellar lesions on brain MRI, 31 had mastoid views on late CUS, and none revealed cerebellar or posterior fossa lesions. Major findings on early and late CUS in relation to outcomes at 18 to 22 months are shown in Tables 4 and 5. Among the 43 cases with adverse early CUS findings, 20 went on to have adverse late CUS findings. Of those with adverse early CUS cases, 32 had grade III ICH only (unilateral or bilateral), of which 11 went on to have adverse late CUS findings. Of the adverse early CUS cases, 11 had grade IV ICH (unilateral or bilateral) as a component of their findings, of which 9 went on to have adverse late CUS findings. Of the 6 cases with adverse late but not adverse early CUS findings, the late CUS findings were as follows: 3 had moderate-severe VE only, 1 had moderate-severe VE and shunt, 1 had cystic PVL, and 1 had porencephalic cyst. Of the 26 children with NDI but without adverse early CUS findings (Table 3), 4 had severe hearing impairment only, 1 had moderate-severe CP only, and 21 had BSID III cognitive score <70 as a component of their NDI. Of these 21, only 2 had adverse late CUS findings, 6 had moderate-severe WMA on MRI, and 6 had significant cerebellar lesions on MRI. Of the 25 children with NDI but without adverse late CUS findings (Table 5), 20 had BSID III cognitive score <70 as a component of their NDI. Of these 20, only 1 had adverse early CUS findings, 5 had moderate-severe WMA on MRI, and 5 had significant cerebellar lesions on MRI. Of the 7 children with significant gross motor function impairment but without adverse late CUS findings (Table 5), 1 had moderate-severe WMA on MRI, and 3 had significant cerebellar lesions on MRI.

In models that included all neuroimaging variables, both late CUS adverse findings and MRI findings of significant cerebellar lesions remained independently associated with NDI or death, and with significant gross motor impairment or death, but not early CUS adverse findings or moderate-to-severe WMA on MRI (Table 6). However, in models with late CUS

**TABLE 1** Demographic, Perinatal and Neonatal Characteristics of the NEURO Follow-up Cohort (*N* = 445)

| Characteristics | |
|---|---|
| Birth weight, mean ± SD, g | 856 (190) |
| EGA, mean ± SD, wk | 25.9 (1.0) |
| Multiple gestation | 102 (22.9) |
| Race | |
| Non-Hispanic black | 141 (31.7) |
| Non-Hispanic white | 192 (43.2) |
| Hispanic | 98 (22.0) |
| Other | 14 (3.2) |
| Boy | 246 (55.3) |
| Any antenatal steroids | 428 (96.2) |
| Cesarean delivery | 306 (68.8) |
| PDA diagnosed | 222 (50) |
| Late sepsis[a] | 144 (32) |
| NEC diagnosed | 32 (7) |
| Severe ROP[b] | 48/412 (12) |
| Surgery for PDA or NEC or ROP | 84 (19) |
| Postnatal steroids[c] | 38 (9) |
| BPD[d] | 159 (36) |
| Neonatal neuroimaging | |
| Early CUS adverse finding (grade III or IV ICH or cPVL) | 43 (9.7) |
| Late CUS adverse finding (moderate or severe VE, cPVL, porencephalic cyst, or shunt) | 26 (5.8) |
| Moderate or severe WMA on MRI | 86 (19.3) |
| Any cerebellar lesions on MRI | 72 (16.2) |
| Significant cerebellar lesions on MRI | 46 (10.3) |

Data presented as *n* (%) unless otherwise specified.

[a] Late sepsis: culture-proven sepsis from 7 d of age to discharge and treated with antibiotics for at least 5 d.

[b] Severe ROP: threshold ROP,[13,16] ophthalmologic surgery, or the use of bevacizumab treatment of retinopathy.

[c] Postnatal steroids: any corticosteroid given for prevention or treatment of BPD.

[d] BPD: receipt of >30% supplemental oxygen at 36 wk or the need for positive-pressure support or, in the case of infants requiring >30% oxygen, the need for any supplemental oxygen at 36 wk after an attempt at withdrawal of oxygen.

**TABLE 2** Relation of WMA Severity on Near Term Brain MRI to Neurodevelopmental Outcomes at 18 to 22 Months

| Outcome at 18–22 mo Corrected Age | Severity of WMA | | | | |
|---|---|---|---|---|---|
| | Normal, *n* = 98 | Mild, *n* = 261 | Moderate, *n* = 68 | Severe, *n* = 18 | *P* |
| Cognitive score, mean ± SD | 93.5 (14.0) | 92.6 (13.1) | 89.9 (15.3) | 77.7 (14.5) | <.0001 |
| Cognitive score <70 | 4/98 (4.1) | 11/258 (4.3) | 7/67 (10.5) | 4/18 (22.2) | .011 |
| Cognitive score <85 | 20/98 (20.4) | 47/258 (18.2) | 20/67 (29.9) | 11/18 (61.1) | .0001 |
| Any CP | 2/98 (2.0) | 14/261 (5.4) | 4/68 (5.9) | 11/18 (61.1) | <.0001 |
| Moderate to severe CP | 0/98 | 3/261 (1.2) | 1/68 (1.5) | 9/18 (50.0) | <.0001 |
| NDI | 4/98 (4.1) | 16/258 (6.2) | 7/67 (10.5) | 11/18 (61.1) | <.0001 |
| Significant gross motor impairment | 1/98 (1.0) | 5/261 (1.9) | 1/68 (1.5) | 10/18 (55.6) | <.0001 |
| Unimpaired/mildly impaired | 69/98 (70.4) | 176/258 (68.2) | 40/67 (59.7) | 3/18 (16.7) | <.0001 |
| NDI or death | 4/98 (4.1) | 25/267 (9.4) | 11/71 (15.5) | 13/20 (65.0) | <.0001 |

Data presented as *n*/*N* (%) unless otherwise specified.

**TABLE 3** Cerebellar Lesions on Near Term Brain MRI and Neurodevelopmental Outcomes at 18 to 22 Months

| Outcome at 18–22 mo Corrected Age | Cerebellar Lesions | | | |
|---|---|---|---|---|
| | No Cerebellar Lesions, *n* = 373 | Any Cerebellar Lesions, *n* = 72 | *P*[a] | Significant Cerebellar Lesions,[b] *n* = 46 |
| Cognitive score, mean ± SD | 93.1 (13.5) | 84.9 (14.8) | <.0001 | 84.2 (15.9) |
| Cognitive score <70 | 15/369 (4.1) | 11/72 (15.3) | .0002 | 7/46 (15.2) |
| Cognitive score <85 | 67/369 (18.2) | 31/72 (43.1) | <.0001 | 20/46 (43.5) |
| Any CP | 18/373 (4.8) | 13/72 (18.1) | <.0001 | 11/46 (23.9) |
| Moderate to severe CP | 6/373 (1.6) | 7/72 (9.7) | .0017 | 7/46 (15.2) |
| NDI | 21/369 (5.7) | 17/72 (23.6) | <.0001 | 12/46 (26.1) |
| Significant gross motor impairment | 8/373 (2.1) | 9/72 (12.5) | .0004 | 9/46 (19.6) |
| Unimpaired/mildly impaired | 256/369 (69.4) | 32/72 (44.4) | <.0001 | 20/46 (43.5) |
| NDI or death | 32/380 (8.4) | 21/76 (27.6) | <.0001 | 16/50 (32.0) |

Data presented as *n*/*N* (%) unless otherwise specified.

[a] *P* values reflect comparisons between no cerebellar lesions and any cerebellar lesions groups.

[b] Significant cerebellar lesions were defined as lesions that were bilateral, cystic, and/or ≥4 mm in size.

excluded, MRI findings of both moderate-to-severe WMA and significant cerebellar lesions remained independently associated both with NDI or death and significant gross motor impairment or death, but again, not early CUS adverse findings. In models with MRI excluded, late CUS adverse findings, but not early CUS adverse findings, remained significant. Of note, CIs are wide because of low frequency of adverse neuroimaging findings and adverse outcomes.

As demonstrated by AUC of the ROC curves (Table 7), compared with models that included only perinatal/neonatal variables, predictive capability of the models was improved by the successive addition of early CUS and late CUS, and was best in models that included MRI. However, of note, 95% CIs around the AUC for these models overlapped.

## DISCUSSION

In the largest study of its kind, we found that adverse near-term brain MRI and late CUS findings among extremely preterm infants were associated with adverse neurodevelopmental outcomes at 18 to 22 months. In multivariable models, both late CUS findings reflective of WM injury and MRI findings of significant cerebellar injury remained independently associated with adverse outcomes. In models that did not include late CUS, MRI findings of both moderate-to-severe WMA and significant cerebellar lesions were independently associated with adverse outcomes. Early CUS findings were not associated with adverse outcomes when any late neuroimaging was taken into account. Our results underscore the need to understand the evolution of brain injury over time in outcomes prediction rather than to rely upon early findings only, and suggest the need to revisit recommendations for neuroimaging in the preterm infant.

Our findings concur with others regarding the relative value of later neuroimaging compared with early CUS alone. The Extremely Low Gestational Age Newborn (ELGAN) study revealed that only when accompanied or followed by WM lesions was intraventricular hemorrhage associated with increased risk for motor or developmental impairment at 2 years.[4] Other preterm cohorts with both CUS and MRI revealed significant associations between MRI findings and outcomes, but assessed CUS only for highest grade of ICH or cPVL rather than for later findings,[8] or determined that any substantial abnormalities on MRI were detected by CUS done on the same day.[26,27] In a study of weekly CUS and

**TABLE 4** Major Early CUS Findings and Neurodevelopmental Outcomes at 18 to 22 Months' Corrected Age

| | Early CUS | | | |
|---|---|---|---|---|
| Outcome at 18–22 mo Corrected Age | Normal, $n$ = 322 | All Without ICH Grade III/IV or cPVL on Early CUS, $N$ = 402 | ICH Grade III/IV or cPVL, $n$ = 43 | $P$[a] |
| Cognitive score, mean ± SD | 92.3 (13.5) | 92.2 (13.7) | 88.0 (16.1) | .06 |
| Cognitive score <70 | 16/319 (5.0) | 21/398 (5.3) | 5/43 (11.6) | .16 |
| Cognitive score <85 | 65/319 (20.4) | 83/398 (20.9) | 15/43 (34.9) | .04 |
| Any CP | 9/322 (2.8) | 17/402 (4.2) | 14/43 (32.6) | <.0001 |
| Moderate to severe CP | 2/322 (0.6) | 5/402 (1.2) | 8/43 (18.6) | <.0001 |
| NDI | 19/319 (6.0) | 26/398 (6.5) | 12/43 (27.9) | <.0001 |
| Significant gross motor impairment | 4/322 (1.2) | 8/402 (2.0) | 9/43 (20.9) | <.0001 |
| Unimpaired/mildly impaired | 217/319 (68.0) | 266/398 (66.8) | 22/43 (51.2) | .04 |
| NDI or death | 27/327 (8.3) | 38/410 (9.3) | 14/45 (31.1) | <.0001 |

Data presented as $n/N$ (%) unless otherwise specified.

[a] $P$ values reflect comparisons between those with and without early CUS composite adverse finding (ICH grade III or IV or cPVL).

**TABLE 5** Major Late CUS Findings and Neurodevelopmental Outcomes at 18 to 22 Months' Corrected Age

| | Late CUS | | | |
|---|---|---|---|---|
| Outcome at 18–22 mo Corrected Age | Normal, $N$ = 321 | All Without Porencephalic Cyst, cPVL, Moderate to Severe VE, or Shunt, $N$ = 419 | Porencephalic Cyst, cPVL, Moderate to Severe VE, or Shunt, $n$ = 26 | $P$[a] |
| Cognitive score, mean ± SD | 92.8 (13.2) | 92.4 (13.5) | 82.0 (18.2) | .0002 |
| Cognitive score <70 | 13/317 (4.1) | 20/415 (4.8) | 6/26 (23.1) | .0024 |
| Cognitive score <85 | 60/317 (18.9) | 84/415 (20.2) | 14/26 (53.9) | <.0001 |
| Any CP | 11/321 (3.4) | 17/419 (4.1) | 14/26 (53.9) | <.0001 |
| Moderate to severe CP | 1/321 (0.3) | 4/419 (1.0) | 9/26 (34.6) | <.0001 |
| NDI | 17/317 (5.4) | 25/415 (6.0) | 13/26 (50.0) | <.0001 |
| Significant gross motor impairment | 4/321 (1.3) | 7/419 (1.7) | 10/26 (38.5) | <.0001 |
| Unimpaired/mildly impaired | 220/317 (69.4) | 281/415 (67.7) | 7/26 (26.9) | <.0001 |
| NDI or death | 22/322 (6.8) | 38/428 (8.9) | 15/28 (53.6) | <.0001 |

Data presented as $n/N$ (%) unless otherwise specified.

[a] $P$ values reflect comparisons between those with and without late CUS composite adverse finding (porencephalic cyst, cPVL, moderate to severe VE, or shunt).

near-term MRI, periventricular echogenicities and peri- and intraventricular hemorrhage were predictive of abnormal WM on MRI, and their absence predicted favorable 2-year outcome.[28] Others have revealed that MRI may provide additive information to predict neuromotor outcomes,[29] complementary to specific findings such as periventricular echodensities by CUS,[30] or neurologic examination.[31,32] Our results suggest that some type of near-term imaging (late CUS or brain MRI) adds value over perinatal/neonatal factors and early CUS alone. Predictive capability as measured by AUC of the ROC was best in models with all neuroimaging, but improvement with the addition of MRI was marginal.

The importance of cerebellar injury in preterm infants has become increasingly recognized in the understanding of brain connectivity, and is associated with neuromotor, behavioral, and cognitive delays.[33,34] The cerebellum can be visualized by CUS with mastoid views, but MRI may allow for a more complete visualization of location and extent of injury. Our findings indicate that cerebellar injury was rarely seen by CUS; however, less than half of all study CUS had mastoid views. Detection could potentially have been improved by requiring mandatory mastoid and cine sequences. Nevertheless, like others[11] we found that cerebellar lesions by MRI were not uncommon, were typically missed by CUS, and the presence of significant cerebellar lesions by MRI was independently associated with adverse outcomes.

Although the limitations of early CUS findings have been reported, it is important to note that a substantial proportion of children with adverse late CUS or MRI findings in our cohort did not have severe adverse outcomes at 18 to 22 months, emphasizing that neuroimaging must not be used in isolation to predict outcomes. In addition, despite the strengths of our study, including a large sample size, serial CUS and near-term MRI, central reading, and a high follow-up rate, there are limitations. The NEURO cohort is a selective subgroup, with low rates of both adverse outcomes and neuroimaging findings that may limit our power to assess associations. The rates of neurodevelopmental impairment are lower than usually reported, although they are consistent with those reported by Skiold, et al.[26] The BSID III has been reported to underestimate developmental delay as compared with the previous edition[35]; this likely explains the lower impairment rates as defined. Neuroimaging study procedures

**TABLE 6** Independent Associations of Neonatal Neuroimaging Findings With 18 to 22 Months' Corrected Age Outcomes

| Neuroimaging Adverse Finding | NDI or Death | | Significant Gross Motor Impairment or Death | |
|---|---|---|---|---|
| | Adjusted OR (95% CI) | *P* | Adjusted OR (95% CI) | *P* |
| Full model | | | | |
| Perinatal/neonatal factors[a] + early CUS + late CUS + brain MRI | | | | |
| Early CUS[b] | 0.7 (0.2–2.4) | .56 | 0.8 (0.2–3.3) | .77 |
| Late CUS[c] | 9.8 (2.8–35) | .0005 | 10.9 (2.5–47.3) | .0014 |
| MRI moderate or severe WMA | 1.5 (0.6–3.6) | .34 | 1.6 (0.5–4.9) | .45 |
| MRI significant cerebellar lesions | 3.0 (1.3–6.8) | .0078 | 5.2 (1.9–14.1) | .0012 |
| Limited models | | | | |
| Perinatal/neonatal factors + early CUS+ brain MRI (excludes late CUS) | | | | |
| Early CUS[b] | 1.8 (0.7–4.6) | .22 | 2.1 (0.7–6.7) | .19 |
| MRI moderate or severe WMA | 2.4 (1.1–5.2) | .024 | 2.8 (1.0–7.6) | .04 |
| MRI significant cerebellar lesions | 2.7 (1.3–5.9) | .01 | 4.5 (1.8–11.6) | .0017 |
| Perinatal/neonatal factors + early CUS + late CUS (excludes MRI) | | | | |
| Early CUS[b] | 1.0 (0.3–3.3) | .96 | 1.2 (0.3–4.6) | .74 |
| Late CUS[c] | 11.9 (3.6–39.8) | <.0001 | 13.2 (3.4–50.8) | .0002 |

[a] Perinatal/neonatal factors included in the model for NDI or death: race, late sepsis, BPD, and postnatal steroids; and included in the model for significant gross motor impairment or death: race, multiple gestation, maternal insurance, late sepsis, BPD, and PNS.

[b] Early CUS composite adverse finding: grade III or IV ICH or cPVL.

[c] Late CUS composite adverse finding: moderate or severe VE, or cPVL, or porencephalic cyst, or shunt.

requiring more frequent and detailed views and sequences might have also resulted in enhanced injury detection by CUS[28,29] and/or MRI.[36,37] For example, more frequent CUSs throughout the hospitalization could have allowed for detection of small WM cysts that may resolve by the time late CUS is performed.[2] Our study called for only 2 CUSs, and included a range of acceptable timing for acquisition. Advanced MRI findings including diffusion tensor imaging and cortical surface area and cerebral volumetric measures among preterm infants have been associated with adverse childhood outcomes, and are suggested as surrogate biomarkers of neuromotor and cognitive impairment. But these more detailed MRI approaches may not be available or clinically interpretable in many settings. We also recognize that the range of accepted PMA at brain MRI was wide, which, although assessed in the context of corpus callosum thinning, may have limited evaluation of delay in myelination. However, our goal in this study was to investigate usual CUS and conventional MRI in a more applicable and generalizable comparison. Finally, outcomes at 18 to 22 months cannot provide a nuanced picture of later childhood. Some recent analyses have revealed associations of WM injury on neonatal MRI with cognitive delay, coordination impairment, and behavioral and psychiatric diagnoses,[9,10,38,39] but such outcomes are complex and influenced by many factors. Thus, presenting neonatal neuroimaging results to families as singular predictive factors, and without a clear context of their limitations, is neither appropriate nor accurate.[40] Whether findings on neonatal brain MRI can help to inform prediction of later childhood end points over and above CUS, other neonatal factors, and postdischarge environment, require further study. Additional investigations are also warranted to determine if potentially improved prediction offered by MRI will be balanced by cost and other challenges, and by perceived value to families and providers. To that end, the NEURO cohort continues to be followed to school age.

**TABLE 7** Classification Statistics for ROC Curve Analyses Based on Stepwise Models

| Outcome | Model Variables | AUC | 95% CI |
|---|---|---|---|
| NDI or death | | | |
| | Perinatal/neonatal | 0.743 | 0.67–0.82 |
| | Perinatal/neonatal + Early CUS | 0.773 | 0.70–0.84 |
| | Perinatal/neonatal + Early + Late CUS | 0.800 | 0.73–0.87 |
| | Perinatal/neonatal + Early CUS + MRI | 0.809 | 0.75–0.87 |
| | Perinatal/neonatal + Early + Late CUS + MRI | 0.825 | 0.76–0.89 |
| Significant gross motor impairment or death | | | |
| | Perinatal/neonatal | 0.833 | 0.75–0.92 |
| | Perinatal/neonatal + Early CUS | 0.859 | 0.79–0.93 |
| | Perinatal/neonatal + Early + Late CUS | 0.885 | 0.82–0.95 |
| | Perinatal/neonatal + Early CUS + MRI | 0.892 | 0.83–0.96 |
| | Perinatal/neonatal + Early + Late CUS + MRI | 0.908 | 0.85–0.97 |

WM injury is an important link to brain development and neurodevelopmental outcomes among very preterm infants.[41] Although severe ICH on early CUS is strongly associated with accompanying or subsequent WM lesions, it is not an absolute relationship. A primary guideline for clinical neuroimaging screening in the United States recommends CUS for all infants younger than 30 weeks' EGA at 7 to 14 days, and only "optimally" again at 36 to 40 weeks.[1] Unfortunately, an early CUS finding of severe ICH or cPVL is frequently the single adverse neuroimaging variable considered in prospective and retrospective studies of preterm neurodevelopmental outcomes, and a primary focus in discussions with families of preterm infants. Based on our findings and those of other

investigators, current routine neuroimaging guidelines for very preterm infants should be reevaluated to recognize the potential limitations of early CUS alone among those surviving to discharge, and to include expanded information and recommendations regarding near-term neuroimaging, both for clinical and research purposes.

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